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NUTRITION REVIEWS

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NUTRITION REVIEWS

VOL. 2 DECEMBER, 1944 No. 12

THE USE AND ABUSE OF VITAMINS IN THE TREATMENT OF MILD OR EARLY DEFICIENCY STATES

No one could possibly question the use of vitamins in the treatment of frank vitamin deficiencies, or even in suspected deficiency states. Yet, one often wonders if the widespread use of vitamins in apparently healthy people, as practiced in this country today, is justified.

In patients having a fullblown deficiency such as pellagra, beriberi, or scurvy, intensive vitamin therapy obviously is indicated at once. Rarely does one see more spectacular recoveries. Within twenty-four hours there is an improvement in the appetite and sense of well-being. After a week to ten days the patient, who may have been moribund on admission, has been restored to health. However, advanced deficiencies, as described above, are becoming less and less frequent and do not constitute a serious problem today.

Less dramatic, but equally gratifying, is the response of the early or mildly deficient patient to treatment with specific vitamins, especially those of the B-complex. A marked improvement in appetite and sense of well-being frequently is noted; the tongue which usually feels to the patient sore and scalded rapidly becomes normal; the fissures in the corners of the mouth heal, and within a short period of time the patient feels like a new person.

In patients with chronic wasting diseases, who may develop secondary deficiencies, or even in those people who have become run down from other causes, vitamin therapy is definitely indicated. Likewise, pre- and post-operative medical care has been greatly improved by the use of vitamins. Patients having serious liver damage have been materially benefited by the parenteral administration of vitamins and in some instances such treatment has even been life-saving. Those subsisting for long periods of time upon restricted diets in the treatment of such disorders as peptic ulcer, allergic conditions, and obesity, also should be given vitamins.

If vitamin therapy has been restricted to the types of patients described above, the question of the abuse of vitamins would never have arisen. Unfortunately, there are those who have argued that such vague symptoms as weakness and fatigability, nervousness, insomnia, irritability, "gas," or indefinite digestive disturbances may result from a vitamin deficiency, and therefore patients having these complaints should receive the benefit of vitamin therapy, even though there is no definite evidence that a deficiency state actually exists. To make matters worse, it has been claimed that vitamin therapy must be continued over a period of months or as long as a year in order to be effective.

Quite naturally those interested in the sale of vitamins have taken up the cry, and at almost any hour of the day, over the radio, one hears a discussion of these various symptoms and is urged to take this or that vitamin preparation, regardless of the diet that has been consumed. As a result, the vitamin bill in this country last year was over $200,000,000, which obviously represents a great economic waste.

Thus, the medical profession finds itself in a dilemma. On the one hand, the importance of vitamins in the maintenance of health and strength must be emphasized. However, it is far more desirable to furnish these accessory food factors by an adequate diet rather than by the use of pills. In fact, an adequate diet is the only satisfactory means of providing a full vitamin intake. The necessity of vitamin therapy in the treatment of frank deficiency states, either mild or advanced, or in conditions such as described above, should be recognized by all.

On the other hand, it is the physician's personal responsibility to prevent his patients from becoming victims of needless and expensive vitamin therapy and to point out that vitamins are not a panacea for all human ills. There are certain principles, which if intelligently followed, will enable one to steer a safe course between the horns of this dilemma.

1. Vitamin therapy is definitely indicated in patients having objective evidence of a deficiency state, but should always supplement dietary treatment, never replace it.
2. Vitamin therapy is useful in preventing the development of secondary deficiencies in chronic wasting diseases and pre- and post-operative medical care.
3. In the absence of organic disease, the individual who consumes a diet, adequate in calories, consisting of fruits, milk, eggs, a variety of meats, and green vegetables does not need additional vitamins.
4. Vague symptoms such as weakness, fatigability, insomnia, nervousness, and irritability, are more apt to be due to overwork, nervous tension, or to social, domestic, or financial difficulties than to a vitamin deficiency.
5. For the most part, prolonged vitamin therapy in the absence of obvious disease is useless.

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DIET AS A PREDISPOSING FACTOR IN RHEUMATIC FEVER

Peete (*Ann. Int. Med.* **21,** *44 (1944)*) accumulated data on diet as a predisposing factor in rheumatic fever. He studied patients with acute rheumatic fever and chronic rheumatic heart disease from the point of view of dietary deficiencies of vitamin D, calcium, and phosphorus. During a period of four years patients seen in both private practice and clinic, showing any signs of rheumatic fever or rheumatic heart disease, were instructed to take daily sun baths when possible and to include one quart of milk, one egg, and cod liver oil in the daily diet. He observed such a marked lowering of the incidence of recurrences of the disease that he undertook a survey of the dietary habits of similar patients before correcting their diets. Data on the diets of 50 patients, some in the acute and some in the chronic rheumatic state, were compared with similar data on the diets of 25 normal schoolchildren in a public school.

The patient was instructed to indicate on a schedule the number of times per month he ate servings of specified foods. The number but not the amount of servings was obtained. Therefore, the diets were not subjected to quantitative analysis. Foods were grouped in the following categories: milk, eggs, fresh meat, bacon, cheese, butter, green vegetables, starch vegetables, citrus fruits, other fruits, and starches. The last item included bread, cereals, macaroni, spaghetti, candy, crackers, cookies, and desserts. The data are presented in the form of a block diagram and indicate that the patients with rheumatic disease consumed much less milk, fresh meat, and green vegetables, slightly less eggs, cheese, citrus fruits, and other fruits than did the normal children. The rheumatic patients consumed many more starchy vegetables and other starchy foods.

Peete reached the conclusion that the average diet of the patient with rheumatic fever and chronic rheumatic heart disease is low in those foods that supply vitamins A and D and the minerals, especially calcium, phosphorus, and iron. He noted also that the diets of the rheumatic patients were deficient in proteins and contained an excess of starchy foods and refined sugars. If it is

assumed that the caloric intake of the rheumatic patients was comparable with that of the normal children, it can be concluded that the patients obtained a greater number of calories from starchy foods and refined sugars and, therefore, the intake of the B-complex vitamins was less for the patients than for the normal children. However, the author does not reach the conclusion that the diets of the patients were deficient in vitamins of the B-complex. The chronically ill patient is prone to develop abnormal dietary habits. Evaluation of the dietary habits of the patient prior to onset of the disease would have been an important contribution to the study.

Socio-economic factors were considered. Peete observed that the average number in the families of 75 rheumatic patients was 7.5 members per family. However, he believed that socio-economic status was not the sole factor, for among his patients some people with adequate incomes were subsisting on impoverished diets. Peete analyzed statistics of the United States Department of Commerce on the incidence of deaths from acute rheumatic fever, chronic rheumatic heart disease, and pellagra and compared these data with statistics of the Bureau of Agricultural Economics on percentages of farms with milch cows and hogs. From the accumulated statistics it appeared that the incidence of acute rheumatic fever and chronic rheumatic heart disease is less in the regions where there are greater numbers of milch cows and hogs. However, the author did not emphasize the fact that the regions having more livestock are also the regions having less density of population, and therefore, providing less opportunity for spread of respiratory infections. Nevertheless, the correlation is an interesting one.

The author was impressed by the acceleration in the downward trend of the death rate from both rheumatic fever and tuberculosis after the discovery of the cause of rickets. There is the possibility that preventive measures taken to lower the incidence of rickets, in addition to the public health measures instituted to control tuberculosis, have been responsible for the lowering of the death rate from rheumatic fever. Consideration was given to the similarity between rheumatic fever and rickets not only in their social incidence and geographic distribution but also in the close relation between the tissues involved in the two diseases. Rheumatic fever involves primarily the mesodermal or the connective tissue of the body, whereas rickets involves the cartilage and bone which are derived from connective tissue. Peete has studied patients with consideration of signs of previous disturbances in mineral metabolism, i.e., dental caries, scoliosis, flaring of the ribs, thoracic deformities known to be acquired, bow legs, and knock knees. He has observed that many rheumatic patients show at least one of these signs and some show evidence of several such disturbances. He concludes from his several observations and dietary surveys that poor diets and lack of exposure to sunshine, with the socio-economic implications of these deficiencies, are the most important predisposing factors in the causation of acute rheumatic fever. Adequate amounts of vitamins A and D, milk, proteins, and the value of sun bathing were especially emphasized in the prevention of rheumatic disease and its sequelae.

One may not accept the degree of importance which Peete has attributed to the nutritional status of vitamin D in causation of susceptibility to rheumatic fever and rheumatic heart disease, for it is likely that the total nutritional status has a more important bearing in resistance to primary infectious diseases and development of immune reactions. It has not been conclusively demonstrated that susceptibility to primary bacterial and virus diseases is increased in the nonimmune person by nutritional deficiency disease. However, there is general clinical acceptance of the opinion that good nutritional status is of distinct advantage to the patient for withstanding ravages of

disease and its complications. It is a common clinical observation that patients who have good nutritional status are better operative risks than patients who are malnourished.

In considerations of nutritional status and disease, factors affecting resistance or immunity to disease must be clearly differentiated from factors affecting resistance to trauma of disease.

DISTILLATION BY-PRODUCTS AS ANIMAL FEEDS

The increase in alcohol production attending the industrial war program has resulted in a large increase in the production of distillers' by-products available as livestock feeds. This supply of feedstuffs is important not only because of otherwise short supplies of feeds for our animal population, but because these by-products are apparently good sources of some of the nutrients otherwise deficient or lacking in many common feedstuffs.

A number of types of fermentation by-products are on the feedstuffs market today. These differ somewhat, depending on the type of material used in the fermentation, the type of fermentation itself, and the treatment given the material after fermentation. Corn, wheat, and molasses are in common use as source materials. In grains, the solid residues are separated from the stillage by screening, and then dried to produce distillers' dried grains. These have been used, mainly in dairy feeds, for many years. The remaining stillage may be handled in different ways. The fine suspended solids may be separated from the liquid fraction by centrifugation, the clarified stillage concentrated by vacuum evaporation, and ultimately dried to produce distillers' dried solubles. The entire stillage, liquid fraction + suspended solids, may be evaporated and dried to produce dried solubles, or in some cases merely concentrated by vacuum evaporation to produce solubles which are marketed in a semisolid form. When molasses is used in the fermentation, the problem of drying the solubles is somewhat more difficult than in the grains. This difficulty may be overcome by drying the solubles, after concentration, on some suitable material, preferably one which is already in common use as a feedstuff. Grain solubles are sometimes added to the distillers' dried grains and marketed as dried grains with solubles added.

Distillers' solubles were formerly a waste product of the industry. Conservation laws prohibiting stream pollution, however, forced the industry, within the past five years, to seek other means of disposal of this material, and led to the development of processing methods to yield products which are acceptable and useful to the feedstuff trade. The nutritive value of these products seems to be well established. Owing to their bulk, the dried grains are well adapted for feeding cattle. The solubles may serve as important sources of water soluble vitamins for poultry, swine, calves, and dogs.

The nutrient content of alcohol fermentation by-products from corn has been reported by Bauernfeind and associates (*Ind. Eng. Chem.* **36,** *76 (1944)*). These authors report the protein content of both the solubles and grains as being about 30 per cent. It is estimated that the dried soluble grain yeast concentrate from corn contains approximately 20 per cent of yeast, and as a source of riboflavin it compares well with dried skim milk. It contains more thiamin, niacin, and biotin and slightly less pantothenic acid than dried skim milk. As determined by the growth of chicks, 8 per cent of corn distillers' dried solubles produced a growth response similar to that obtained by solubilized liver. However, chicks which received the liver had a higher

hemoglobin level and a better feather appearance than those fed the distillers' by-product. The fat soluble vitamin content of dried corn solubles is relatively low. The protein of this product is probably not biologically complete but it has, undoubtedly, a definite supplementary value. The mineral content of dried corn solubles is somewhat higher than corn, but they are subject to the same limitations as corn. Corn distillers' dried grains are bulky and are thus well suited for cattle. They are rich in protein and fat, but low in water soluble factors. The addition of solubles to the dried grains improves the product from this viewpoint.

A variable mash bill (composition of mash), incorporating corn at one extreme and wheat at the other, produces fermentation by-products of a somewhat variable composition. Wheat distillers' by-products, however, have the same approximate vitamin content (excluding the carotenoids) as the corn products, but have a higher protein content and less fat.

Studies of the nutritive value of corn distillers' by-products for poultry have been reported by a number of workers. These reports have been summarized by Bauernfeind and Boruff (*Am. Miller* **72,** *no. 1, p. 182; no. 2, p. 53; no. 3, p. 50 (1944)*). It is apparent that dried corn solubles are suitable for poultry in amounts from 2 to 5 per cent of the ration. Their suitability has been demonstrated for chick starting rations, growing rations, and for egg production and hatchability. The results obtained are, in general, comparable to those obtained with skim milk. Growth, fleshing, feather development, leg coloring, hatchability, and food utilization indicate that corn dried grains may replace part of the cereal grains in a poultry ration. It is apparent that large amounts of both corn solubles and dried grains may possess laxative effects for poultry, but this disturbance is not evident at the levels usually fed. Wheat distillers' dried solubles have given as satisfactory results as the corn product in practical poultry rations. Although other factors may be contributed to the ration, riboflavin is one of the chief attributes of distillation by-products for poultry.

Fairbanks, Krider, and Carroll (*J. Animal Sci.* **3,** *29 (1944)*) and Krider, Fairbanks, and Carroll (*Ibid.* **3,** *107 (1944)*) have reported experiments which demonstrate the value of distillers' by-products for growing pigs. A basal ration made up of corn, wheat, flour middlings, soybean meal, tankage, fish meal, minerals, and cod liver oil was found to be inadequate for growing pigs, and was greatly improved by the addition of either 6 per cent of dried corn distillers' solubles or 12 per cent of corn distillers' dried grains. Pigs fed the fortified rations up to weaning time, and then changed to the basal ration, showed a carry-over or residual effect of factors supplied by the supplemented ration.

The fortification of a basal lactation ration with 6 per cent of distillers' dried solubles did not result in measurable differences in either sows or pigs up to weaning time. However, during the growing-fattening period, supplements of 6 per cent of solubles or alfalfa meal improved the ration to a marked degree. With both sows and pigs receiving the basal ration, only 50 per cent of the pigs survived. Ninety-four per cent of the pigs survived when the basal ration was supplemented with 6 per cent of dried solubles. The factors involved in the improvement of these swine rations are unknown. Apparently known vitamin factors are not involved or are not available to the pig in common feed mixtures. It is apparent, however, that such factors are supplied, at least in part, by corn distillers' solubles and dried grains.

The feeding of distillers' dried grains to cattle is a long-accepted practice. Such products are economical for dairy cattle and under certain conditions may be used in steer feeding. The feeding of wet

stillage to both of these classes of livestock is not a new practice. However, when such stillage comprises a high proportion of the food intake, vitamin A deficiency must be avoided by the use of a good roughage or fish oils.

The 1943 production of distillers' dried grains was over twice that for the year 1938. Distillers' dried solubles for the feedstuffs trade were first produced in 1939. In 1943 the production of solubles was approximately 28,000 tons. Unlimited supplies of these materials will never be available, but it appears that they will be valuable components of the types of rations in which high nutritive quality is required.

RELATIONSHIP OF CHOLINE, BETAINE, AND OTHER COMPOUNDS IN NUTRITION

One of the most fruitful fields of investigation in recent years has been that of the metabolic relationship of such compounds as methionine, cystine, choline, and creatine and the roles which they play in intermediate metabolism. The results of the researches in this field are of interest not only to the biochemist and the physiologist but to the nutritionist as well. A single substance in the diet may replace or spare several others and the level of any one which is necessary for dietary adequacy is determined by the presence and abundance of these related compounds.

A metabolic relationship between choline and methionine was indicated by the discovery of du Vigneaud, Chandler, Moyer, and Keppel (*J. Biol. Chem.* **131,** *57* (*1939*)), that methionine deficient rats can utilize homocystine for growth when choline is present in the diet. From the structure of these compounds it appeared that the chemical reaction involved was one of transmethylation—the transfer of a methyl group from choline to homocystine to form methionine. It has since been established that transmethylation is a general metabolic process. Du Vigneaud and co-workers (*Ibid.* **140,** *625* (*1941*)) demonstrated that the methylation of homocysteine to methionine is reversible and the methionine can serve as a precursor of choline by donating methyl groups to ethanolamine. They showed, also, that methionine may donate a methyl group to guanidoacetic acid to form creatine. This latter reaction appears not to be reversible. Since guanidoacetic acid may be formed from arginine and glycine (Bloch and Schoenheimer, *Ibid.* **138,** *167* (*1941*)), creatine synthesis in the body can now be completely visualized. Our knowledge of the metabolic synthesis of choline was further advanced by the work of Stetten, who showed, by the use of isotopes that the necessary ethanolamine may arise from glycine (*Ibid.* **140,** *143* (*1941*)) or from serine (*Ibid.* **144,** *501* (*1942*)).

Although it was known from the earlier work of Tarver and Schmidt (*Ibid.* **130,** *67* (*1939*)) and others that cystine could be formed metabolically from methionine, the exact mechanism was not clear. It now appears that there is a close connection between this process and those governing the formation of choline and creatine. The work of du Vigneaud, Brown, and Chandler (*Ibid.* **143,** *59* (*1942*)) and Binkley and du Vigneaud (*Ibid.* **144,** *507* (*1942*)) indicates that the demethylated portion of the methionine molecule may couple with serine to form a mixed thioether and that the subsequent cleavage of this thioether yields the reduced form of cystine as one product. These reactions may be visualized as follows:

Methionine ⟶ Methyl + Homocysteine
Homocysteine + Serine ⟶ Thioether
Thioether ⟶ Cysteine ⟶ Cystine

The coupling of homocysteine with serine to yield the thioether appears to be irreversible.

The story of choline, methionine, creatine,

and cystine may be summarized as follows: (1) ethanolamine is formed from glycine or serine, (2) guanidoacetic acid is formed from arginine and glycine, (3) methionine may methylate ethanolamine to form choline (a reversible reaction), or (4) may methylate guanidoacetic acid to form creatine (an irreversible reaction) and (5) homocysteine (demethylated methionine) reacts (irreversibly) with serine to form a thioether, which yields cystine (through cysteine).

These metabolic reactions are of considerable importance from the point of view of nutrition. No diet can be considered low in choline or creatine unless methionine-containing proteins also are restricted. (Theoretically it should be possible to achieve the same end by limiting the dietary intake of ethanolamine or guanidoacetic acid and their precursors. This has not been accomplished in practice. If transmethylation could be blocked, one might obtain a state of choline deficiency in the presence of methionine, but this also has not been achieved.) On the other hand, it is quite possible to have a methionine-deficient diet in the presence of excess cystine, creatine, or choline. Cystine and creatine cannot replace methionine because the chemical reactions mentioned in the previous paragraph are irreversible. Excess choline in a methionine-deficient diet does not replace this amino acid because of the absence of homocystine in most diets.

Two compounds, closely related structurally to choline, have been of value in studying the role played by choline in animal nutrition and physiology. These compounds are betaine and arsenocholine. Betaine differs from choline by the replacement of the terminal alcohol group by a carboxyl group and the loss of water to form an anhydride. Arsenocholine differs from choline in that it has arsenic in place of nitrogen.

Best and Huntsman (*J. Physiol.* **75,** *405* (*1932*)) showed that betaine could replace choline in the prevention and cure of fatty livers. Du Vigneaud, Chandler, Moyer, and Keppel (*J. Biol. Chem.* **131,** *57* (*1939*)) demonstrated the effectiveness of betaine in making homocystine a dietary substitute for methionine, and Griffith and Mulford (*J. Am. Chem. Soc.* **63,** *929* (*1941*)) showed that it would prevent hemorrhagic degeneration of the kidneys. It was generally assumed that betaine was effective because of its direct reduction to choline but Stetten has presented strong evidence to indicate that the major route whereby the animal handles betaine is demethylation to glycine and that its activity is ascribable to its role as a donor of methyl groups. As a methylating agent it is able to form methionine from homocysteine and choline from ethanolamine. All of these investigators used the rat as the experimental animal.

Welch (*J. Biol. Chem.* **137,** *173* (*1941*)) introduced the arsenic analogue of choline and showed it to be active in the biosynthesis of phospholipids in the rat or mouse. The arsenic served to "tag" the molecule. Arsenocholine proved to be capable of replacing choline in so far as its lipotropic activity is concerned, but was found to be inactive as a donor of methyl groups (Moyer and du Vigneaud, *Ibid.* **143,** *373* (*1942*)). Welch and Landau (*Ibid.* **144,** *581* (*1942*)) presented further evidence that arsenocholine enters into the synthesis of phospholipids as a structural component replacing choline. They also suggested that the intact molecule of choline, rather than its labile methyl groups, is responsible for its lipotropic action.

The importance of choline in the nutrition of the chick was indicated by the work of Abbott and deMasters who reported (*J. Nutrition* **19,** *47* (*1940*)) that a choline deficiency decreases egg production, causes abortion of egg yolks, and induces a high mortality rate, and by Jukes (*J. Biol. Chem.* **134,** *789* (*1940*)), who showed that choline is necessary for growth of chicks and young turkeys and that it prevents perosis or "slipped tendons" in these birds.

When the study of compounds related to

choline was carried to the chick or poult, a number of metabolic differences between the bird and the rat were discovered. It was found that methionine cannot replace choline for chicks (Jukes, *J. Nutrition* **22,** *315 (1941)*; Record and Bethke, *Poultry Sci.* **21,** *271 (1942)*) or poults (Jukes, *Ibid.* **20,** *251 (1941)*) presumably because of its failure to act as a donor of methyl groups. The value of betaine in the bird has been somewhat controversial. McGinnis, Norris, and Heuser (*Proc. Soc. Exp. Biol. Med.* **51,** *293 (1942)*) reported that it was effective in promoting growth, preventing perosis, and reducing mortality in chicks, while Jukes and Welch (*J. Biol. Chem.* **146,** *19 (1942)*), using a different diet, found it to have a slight growth-promoting activity, but to be ineffective in preventing perosis. Jukes and Welch found arsenocholine, on the other hand, to be an effective antiperotic agent.

Almquist and Grau (*J. Nutrition* **27,** *263 (1944)*) have presented evidence in support of the view that betaine is itself physiologically important to the chick. They conclude that betaine (or methionine) is capable of assuming a certain portion of the functions of choline and that arsenocholine is capable of assuming the remainder of the choline functions in the chick. An earlier report by Grau and Almquist (*Ibid.* **26,** *631 (1943)*) is supplementary and the two will be considered together.

Chicks were maintained on a low-choline diet for sixteen to twenty-one days from hatching to deplete them of choline. After the depletion period the chicks, which showed a high incidence of incipient perosis, were banded, weighed, and segregated into groups of three or four, carefully selected for weight gain and vigor. These choline-depleted chicks were then fed a synthetic-type diet in which the protein was one isolated from soybeans, of known low methionine and cystine content (0.25 and 1.5 per cent, respectively). The compounds to be tested were incorporated in this diet singly or with one or more other compounds and each experiment lasted one week. Weight gains were recorded and are reported as average per cent gains per day.

The experimental diet contained inadequate amounts of choline and of cystine and methionine. The limiting factor for growth proved to be the sulfur-containing amino acids despite the choline-deficiency state of the chicks. The growth rate on the unsupplemented experimental diet was 1.2 per cent per day and it was not increased by the addition of choline alone. Cystine or homocystine increased the growth rate of the experimental diet to about 2.0 per cent per day, and if both were added together there was no further stimulation of growth. It appears, therefore, that homocystine can be converted to cystine in the chick, as in the rat. Supplementary methionine with or without the other sulfur-containing amino acids brought the growth rate to 4.3 per cent per day. From this it is evident that methionine completely replaces cystine and adds a growth effect not obtainable by cystine and homocystine. The effect of choline with cystine, with methionine, and with homocystine must be considered separately. With cystine, choline brought the growth rate to 4.0 per cent. With methionine or homocystine, however, the growth rate was increased to about 6.3 per cent which compares well with 7.5 per cent per day on a practical ration. From these experiments, two additional facts emerge: (1) the growth effects of choline and of methionine are distinct from each other and are additive and (2) homocystine can replace methionine in the presence of choline. It is to be presumed that this replacement is possible because choline methylates homocysteine to form methionine, as in the rat. The failure of methionine to replace choline distinguishes the chick from the rat and confirms the earlier work of other investigators.

Betaine, when given with the experimental diet as the only supplement, had little or no growth-promoting effect. This result was to be expected since the first growth-limiting deficiency is one of the sulfur-con-

taining amino acids. When homocystine or cystine was supplied, however, betaine almost completely took the place of methionine. This is indicated by a growth rate of 3.4 per cent and of 4.1 per cent respectively, when betaine was given with cystine and with homocystine. Arsenocholine with cystine or homocystine gave a growth rate of about 4.0 per cent per day, and betaine, homocystine, and arsenocholine together one of 6.6 per cent per day.

Almquist and Grau, in discussing these data, present the concept that betaine (or methionine) provides growth-promoting effect B (betaine effect), that arsenocholine provides growth-promoting effect A (arsenocholine effect), and that choline provides both effects. It is stated that each effect is undoubtedly multiple in nature. The authors postulate further that betaine is physiologically important to the chick and suggest that betaine may be formed in the chick from choline or methionine.

A combination of arsenocholine, betaine, and cystine was not tested in the absence of homocystine. As in the simpler case of betaine + cystine, synthesis of methionine by transmethylation would appear to be impossible because of the lack of homocystine. Attainment of maximal growth with such a combination therefore would give further support to the postulate that betaine as such has physiologic importance. This is nevertheless a most interesting and inviting hypothesis and will undoubtedly stimulate further investigation both in the chick and in other species of animals.

NUTRITION OF THE HAMSTER

Several characteristics of the Syrian hamster suggest its possible suitability as a laboratory animal. Its mature weight rarely exceeds 135 g., the period of rapid growth is short, and its food consumption is less than that of the rat. The hamster has already been found useful in the study of human virus diseases, and there are indications that it may prove to be of value in nutritional studies as well. Reports concerning its dietary requirements have appeared from three different laboratories within the past few years.

Routh and Houchin (*Federation Proceedings* **1**, *191* (*1942*)) reported on five vitamins of the B-complex. They found thiamin, riboflavin, pyridoxine, pantothenic acid, and niacin each to be essential for the growth of the hamster. Polyneuritis developed in these animals within twelve days on a thiamin deficient diet. Three micrograms of thiamin daily by the oral route cured the polyneuritis within two days and produced good growth. Riboflavin deficiency caused loss of weight and death within twenty days, with dermatitis around the mouth and diarrhea occurring in some of the deficient animals. With daily oral doses of 4 micrograms of riboflavin the deficiency signs disappeared and growth was resumed. A deficiency of pyridoxine caused an acrodynia-like dermatitis around the mouth after twelve days and loss of weight and death within twenty-four days. Three micrograms of pyridoxine daily cured the dermatitis in ten days and produced moderate growth. On a pantothenic acid deficient diet, a red encrustation appeared about the mouth, there was loss of weight, and death ensued within twenty days. More than 15 micrograms of pantothenic acid daily were necessary for growth. Niacin deficiency was manifested by rough, stringy fur, alopecia, and an abnormal mouth condition. Loss of weight and death followed. Most of the deficiency signs disappeared when 100 micrograms of niacin were given daily.

Cooperman, Waisman, and Elvehjem (*Proc. Soc. Exp. Biol. Med.* **52**, *250* (*1943*))

studied the requirements of the hamster for several of the water soluble vitamins. They were unable to confirm the findings of Routh and Houchin that niacin is a dietary essential for this species but found indications of a need for biotin and also for p-aminobenzoic acid or inositol or both. Animals receiving a purified diet with a supplement of thiamin, riboflavin, pyridoxine, pantothenic acid, niacin, ascorbic acid, p-aminobenzoic acid, inositol, choline, and a biotin concentrate grew well and developed to maturity. A few females were carried through reproduction with fair success. No diminution in growth rate and no deficiency signs were observed when niacin and ascorbic acid were omitted from the supplement. Biotin deficient animals developed a characteristic dermatitis at the corners of the mouth, the growth rate was distinctly subnormal, and a number of the animals died between the third and fifth week of the experiment. If the animals lived beyond six weeks, the dermatitis became fairly extensive. When biotin was given but p-aminobenzoic and inositol were withheld, the animals "did poorly" and one-third to one-half died within four weeks. Whether the deficiency signs resulted from a lack of both substances or of one alone was not determined. Thiamin, riboflavin, pyridoxine, pantothenic acid, and choline were given to all the experimental animals and the authors drew no conclusions as to the essential nature of these factors.

The results presented by Hamilton and Hogan (*J. Nutrition* **27,** *213 (1944)*) concerning the growth requirements of the hamster are only partially in agreement with those of the other two groups of investigators. They found thiamin, riboflavin, pyridoxine, and pantothenic acid to be essential but could find no evidence of a need for niacin, biotin, inositol, or p-aminobenzoic acid. They added vitamin E, vitamin K, and choline to the list of vitamins investigated and reported that of these, vitamins E and K are essential.

On vitamin E deficient diets, the growth rate of the hamsters was normal at first, then gradually declined. Of 28 animals on experiment, all collapsed. Six were treated and recovered and the other 22 died. Until less than two hours before death slow gain or loss of weight was the only deficiency sign. During the terminal period the animals became unusually active and began to run about the cage, jump in the air, roll over, and bite themselves. They showed a lack of coordination and a violent reaction to external stimuli such as touch or noise. There was a copious flow of saliva. The intensity of these manifestations increased and about an hour before death the animals collapsed and lay in a stupor. Seven of them were treated in this final stage, each with 5 mg. of alpha-tocopherol. One died within a few minutes but the other 6 made spectacular recoveries and were able to move about the cage within an hour.

The animals on vitamin K deficient diets showed a period of arrested growth between the third and seventh week of the experiment. They became thin and presented an unthrifty appearance, and at this stage 3 representative animals showed a considerable number of small hemorrhagic areas in the muscles, subcutaneous tissues, and in the lining of the abdominal cavity. Free blood was found in the sinuses. The animals so affected showed a spontaneous and uneventful recovery. The authors suggest that this spontaneous recovery is explainable on the basis of the establishment of an intestinal flora which is able to synthesize vitamin K.

Hamilton and Hogan also studied the requirements of the hamster for reproduction and lactation. They found inositol to be necessary for the delivery of living young, and niacin and choline necessary for successful lactation. Some evidence for the need of biotin and p-aminobenzoic acid was obtained but the authors consider it insufficient to allow definite conclusions to be drawn. On inositol deficient diets several

females died during or shortly after parturition with one or more decomposed embryos in the uterus. Of 25 litters, 20 were stillbirths. It is assumed by the authors that the 5 females which bore living young had been insufficiently depleted of the inositol reserves. When either choline or niacin was omitted from the breeding diets, small but apparently normal litters were born. Most of the young, however, died within one week. Females given vitamins A, D, E, and K, thiamin, riboflavin, pyridoxine, pantothenic acid, niacin, choline, inositol, biotin, and p-aminobenzoic acid usually bore one litter but few bore a second. From this fact the authors conclude that hamsters require at least one unrecognized vitamin for reproduction.

No explanation is at hand for the discrepancies between the results of the three groups of investigators. Hamilton and Hogan suggest that the basis may be found in the interrelationships between p-aminobenzoic acid, inositol, biotin, and vitamin K in determining the rate at which vitamins are synthesized in the intestinal tract.

IMPROVEMENT IN DENTITION OF LONDON SCHOOLCHILDREN

While the precise role of diet in determining tooth structure and resistance to caries remains to be defined, the importance of nutritional factors as controlling predisposing causes of dental disease has gained increasing acceptance. Some of the more recent observations supporting this opinion have already been reviewed (*Nutrition Reviews* **1,** *5* (*1942*); **2,** *35* (*1944*)). Much of the interest, and at times controversy, in this field has been stimulated by the investigations in the laboratory and on children which have been carried on by Mellanby since 1917.

Mellanby and Coumoulos (*Brit. Med. J.* **1,** *837* (*1944*)) report a definite improvement in the tooth structure and a definite decrease in the incidence of caries in a group of 5 year old London schoolchildren examined in a large scale survey in 1943, as compared to a similar group examined by the same methods in 1929. They discuss the evidence for believing that the improvement may be attributed largely to changes in eating habits which have been developing in recent years.

The examinations were conducted in London County Council Schools in the same neighborhood in both periods. Unselected 5 year old children were examined, as these children had not come under the full influence of the school dental service. The surface structure of the enamel, with degrees of M-hypoplasia classified in three grades, and presence and extent of caries, as revealed by probe and mirror examination, were recorded uniformly for each period. Over 1600 children were examined in 1943 and about 1300 in 1929.

The surface structure had been classified as very defective in 58 per cent of the children in 1929, as contrasted with 33 per cent in 1943. In 1943, 47 per cent showed some M-hypoplasia as contrasted to 34 per cent in 1929, and the numbers showing slight defects were 18 per cent in 1943 compared to 8 per cent in 1929. None of the children in the first period and only 1 per cent in the second period had a full complement of perfectly calcified teeth. The differences with respect to the incidence and degree of dental caries were more striking. The percentage of children with no tooth decay was 22 per cent in 1943, 5 per cent in 1929. Only 29 per cent showed much caries in 1943 as contrasted with 63 per cent in 1929; of those in this category, only 6 per cent of the 1943 children fell into the very bad caries group, as compared with 54 per cent of the 1929 children. In both of the investigations the amount of caries varied considerably from one school to

another. When the schools were classified according to their level in the social scale, in 1943 there was distinctly less caries in the highest grade than in the other three grades, which differed little among themselves. In 1929 there was a tendency for the incidence of caries to increase from the better to the poorer schools.

The picture of a general improvement in deciduous tooth structure and a decrease in the occurrence and degree of caries in the deciduous teeth in the fourteen year interval between these examinations is unequivocal. The case for attributing this improvement to bettering of the diet rests on changes in food habits which have increased the intake of calcium, phosphorus, and vitamin D. On the basis of animal and clinical investigation, Mellanby believes these are the most important dietary factors affecting tooth structure and retarding the onset and spread of dental caries (*Med. Res. Council Special Report Ser., no.* **140** (*1929*); *no.* **153** (*1930*); *no.* **191** (*1934*)). Government efforts to improve the nutrition of pregnant women, infants, and young children through advice in prenatal and infant hygiene clinics have been increasing in the last quarter of a century. The reduction of rickets, so common in the 1920's, to a comparatively rare disease in England is cited as evidence of the probable increased use of vitamin D preparations and the increased consumption of milk. However, the teeth of the children who were 5 years old in 1943 were formed mainly in the immediate prewar years and the first year of the war. More specific factors operating to improve the diets of these children and their mothers were, first, the cheap milk program inaugurated by the Milk Marketing Board in 1934 whereby two thirds of a pint of milk was furnished at very low cost to all children, and, second, the wartime food policy which provided (1) priority on milk allowances together with fruit juices and cod liver oil to pregnant and lactating women, to infants, and to young children, (2) fortification of all margarine with vitamin A and D, and (3) the enrichment of bread with calcium carbonate.

The authors recognize the hazard of attributing the improvement in dental health over a period of years to a concomitant bettering of food habits when unquestionably many other influences have been brought to bear on child life in London during these years. They believe that the experimental evidence that tooth structure is controlled largely by adequate amounts of vitamin D, calcium, and phosphorus is so strong that the improvement in this respect can be reasonably adduced to changes in the dietary in the immediate prewar and early war period. Although investigation has indicated that children's teeth of good structure are less likely to decay than those of poor structure, the reduction of caries observed in this study was greater than would be expected on the basis of improved structure alone. What other contributory factors, nutritional or otherwise, were operating cannot be assessed adequately.

In itself, this study is open to the criticism that associated changes over a period of time do not necessarily signify a cause and effect relationship. However, it is bulwarked by the observations of Mellanby and others under controlled conditions indicating improvement in dental structure, and to a lesser degree a reduction in the incidence of caries, resulting from certain dietary factors. As such, it presents heartening evidence that some of the large-scale measures undertaken to improve the dietary habits of certain segments of the population can be expected to result in an improvement of dental health. At the same time the incidence of defective and decayed teeth found in the second survey serves to emphasize the magnitude of the problem of dental caries and the fact that these are only the first steps in attacking the problem, even though they seem to be in the right direction.

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